Critical Care Explorations
July 2025 • Volume 7 • Number 7 • e1290

OBSERVATIONAL STUDY

OPEN

Evaluation of Hydrocortisone Discontinuation Strategies in Septic Shock: A Retrospective Cohort Study

Hanine O. AlMubayedh, PharmD, BCPS, BCCCP[1]

Rayd A. AlMehizia, PharmD, BCCCP[1]

Abdul Salam, PhD[2]

Razan M. AlGhunaim, PharmD, BCCCP[1]

Othman Mohammed, MD[3]

Abdullah A. Alrbiaan, MD[3]

Nada S. AlQadheeb, PharmD, BCCCP, FCCP, FCCM[4]

IMPORTANCE: While corticosteroid administration in septic shock has been shown to reduce vasopressor requirements and accelerate shock reversal, the optimal discontinuation strategy remains unexplored.

OBJECTIVES: The purpose of this study was to assess whether rates of hemodynamic instability differ among patients with septic shock undergoing abrupt hydrocortisone discontinuation compared with gradual tapering.

DESIGN, SETTING, AND PARTICIPANTS: A retrospective cohort study conducted in five medical and surgical ICUs at a tertiary care hospital, involving adult patients (≥ 18 yr) with septic shock who received at least 48 hours of stress-dose hydrocortisone (≥ 200 mg/d).

MAIN OUTCOMES AND MEASURES: The primary outcome was hemodynamic instability, defined as vasopressor reinitiation during tapering or within 72 hours of hydrocortisone discontinuation. Secondary outcomes included dysglycemia, duration of mechanical ventilation, ICU and hospital length of stay, and mortality.

RESULTS: Patients were grouped based on their hydrocortisone discontinuation strategy into abrupt and gradual tapering groups. A total of 414 patients were included in this evaluation. Gradual tapering was associated with higher rates of hemodynamic instability (29.2% vs. 12.9%; $p < 0.001$), more frequent dysglycemia (59.4% vs. 43.1%; $p < 0.001$), longer hydrocortisone use (9.9 vs. 4.1 d; $p < 0.001$), and extended mechanical ventilation (20 vs. 15 d; $p = 0.014$) and ICU stay (23 vs. 17 d; $p = 0.008$). Total hydrocortisone duration was the strongest independent predictor of post-discontinuation hemodynamic instability, regardless of strategy (adjusted odds ratio, 1.083; 95% CI, 1.025–1.145; $p = 0.004$).

CONCLUSIONS AND RELEVANCE: While abrupt hydrocortisone discontinuation was associated with fewer ICU-related adverse events, hydrocortisone duration was the primary factor influencing hemodynamic instability post-discontinuation among patients with septic shock. Prospective studies are needed to determine the optimal discontinuation strategy in septic shock.

KEYWORDS: glucocorticoids; hemodynamic instability; hydrocortisone; septic shock

Septic shock is a life-threatening condition characterized by an abnormal immune response to infection, leading to metabolic disturbances, organ dysfunction, and cardiovascular instability (1, 2). Despite therapeutic advancements, septic shock remains a leading cause of death in critically ill patients, with mortality rates reaching as high as 80% (3).

Septic shock management centers on early fluid resuscitation, broad-spectrum antibiotics, and vasopressors to restore hemodynamic stability and

Copyright © 2025 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000001290

SHOUT
SHARE
IT

KEY POINTS

Question: What are the differences in rates of hemodynamic instability, clinical outcomes, and complications among septic shock patients undergoing abrupt vs. gradual hydrocortisone discontinuation?

Findings: Abrupt hydrocortisone discontinuation was associated with fewer episodes of hemodynamic instability, reduced total corticosteroid duration, shortened ICU stays, and lowered the incidence of dysglycemia, particularly in diabetic patients, compared with gradual tapering. Total hydrocortisone duration was identified as the primary independent predictor of post-discontinuation hemodynamic instability, regardless of the discontinuation strategy used.

Meaning: Abrupt discontinuation of corticosteroids may offer clinical benefits in septic shock patients while minimizing risks associated with prolonged corticosteroid exposure.

tissue perfusion. Additional measures, such as source control and supportive therapies, are also critical to improving outcomes (4). Corticosteroids have been used as adjunctive therapy in septic shock for over 50 years, with studies showing benefits in reducing vasopressor requirements and accelerating shock reversal. However, their impact on mortality remains unclear (5–8). The efficacy of corticosteroids is believed to stem from their ability to increase adrenergic receptors, prevent desensitization, and enhance catecholamine effects (9, 10). Consequently, the administration of steroids in septic shock may serve to mitigate this state, contributing to the observed benefits of vasopressor reduction and shock reversal.

While recommendations from the 2021 Surviving Sepsis Campaign (SSC) (4) and the 2024 Society of Critical Care Medicine (SCCM) focused update (11) advocate the use of steroids in septic shock, they do not define the optimal duration of therapy or the preferred method of discontinuation. The 2021 SSC guidelines suggest IV hydrocortisone at a dose of 200 mg/d for vasopressor-dependent septic shock unresponsive to fluids and moderate to high-dose vasopressors (4). However, specific guidance on the duration of therapy or discontinuation strategies was removed in the latest update. Similarly, the 2024 SCCM focused update suggests administering corticosteroids to adult patients with septic shock, based on a conditional recommendation and low-certainty evidence. While no specific agent or dosing regimen is endorsed, most studies have used IV hydrocortisone at 200–300 mg/d, administered in divided doses or as a continuous infusion for 5–7 days, with or without tapering (11).

Current evidence comparing abrupt discontinuation and gradual tapering of steroids in septic shock is limited to two small retrospective studies. Sobolewski et al (12) evaluated 87 patients with septic shock, finding higher rates of hemodynamic instability and worse glycemic control in the tapering group compared with abrupt cessation. Similarly, Carabetta et al (13) examined 148 patients with septic shock and observed increased hemodynamic instability with tapering, although this difference did not reach statistical significance. However, after adjusting for fludrocortisone use, baseline mean arterial pressure, and vasopressor duration, abrupt discontinuation reduced the risk of vasopressor reinitiation but increased the incidence of hyperglycemia (13). Notably, neither study accounted for hydrocortisone duration as a variable influencing hemodynamic instability, and both also excluded patients receiving chronic corticosteroid therapy before the initiation of hydrocortisone for septic shock.

Given the current gaps in the literature, our study sought to compare the odds of hemodynamic instability among patients with septic shock undergoing abrupt vs. gradual hydrocortisone discontinuation while accounting for total hydrocortisone duration, chronic corticosteroid use, fludrocortisone use, and vasopressor needs at a tertiary care hospital in Riyadh, Saudi Arabia.

MATERIALS AND METHODS

Study Design, Setting, and Participants

A retrospective cohort study was conducted across five medical and surgical ICUs at a single center providing tertiary-level care to Saudi nationals and citizens in Riyadh, Saudi Arabia. Adult critically ill patients, prescribed hydrocortisone for septic shock from January 2021 to December 2023, were screened for possible enrollment.

Institutional Review Board (IRB) approval was obtained before study initiation on March 28, 2024

(Research Advisory Committee [RAC] No. 2241103) for the study titled "Evaluation of Hydrocortisone Discontinuation Strategies in Resolved Septic Shock: A Retrospective Cohort Study." All procedures were conducted in accordance with the ethical standards of the institutional committee on human experimentation and with the 1975 Helsinki Declaration and its later amendments.

The study protocol was approved by the IRB (RAC No. 2241103) on March 28, 2024, for the study titled "Evaluation of Hydrocortisone Discontinuation Strategies in Resolved Septic Shock: A Retrospective Cohort Study." The IRB provided a waiver of informed consent, and all study procedures were conducted in accordance with the IRB and the Helsinki Declaration of 1975.

Patients were included if they were 18 years old or older, hospitalized in a critical care unit, and had a documented diagnosis of septic shock based on the treating physician's assessment as recorded in the medical records, supported by the *International Classification of Diseases* code R65.21 (severe sepsis with septic shock). Additionally, eligible patients must have received at least one vasopressor and been initiated on stress-dose steroids, defined as a minimum of 200 mg/d of IV hydrocortisone for at least 48 hours. Patients were excluded if hydrocortisone was tapered or discontinued before vasopressor discontinuation, died before hydrocortisone tapering or discontinuation, or had concurrent shock syndromes such as hemorrhagic, obstructive, cardiogenic, neurogenic, or anaphylactic shock.

Patients were grouped into gradual tapering or abrupt discontinuation groups based on the hydrocortisone discontinuation strategy. The abrupt discontinuation group was defined as patients who received stress-dose hydrocortisone followed by discontinuation without any dose reduction or change in administration time intervals. At the same time, gradual taper group was defined as patients who received stress-dose hydrocortisone and underwent subsequent dose reduction or change in administration time intervals for at least 2 days (12, 13).

At the time of this retrospective review, no standardized protocol for corticosteroids withdrawal was in place, and the decision to discontinue steroids was left to the discretion of the physician. The hydrocortisone regimen followed at the study center consisted of 50 mg administered IV every 6 hours, occasionally preceded by a 100 mg bolus dose at the start of the therapy.

Data Collection

Data were collected through retrospective chart review of the electronic medical records. The Research Electronic Data Capture electronic tool was used to optimize data management (14). Data collected included patient demographics, such as age, gender, body mass index, and chronic comorbidities. Clinical data included chronic corticosteroid use defined as steroid use for more than or equal to 1 month, indication for chronic corticosteroid chrouse, Sequential Organ Failure Assessment (SOFA) score at ICU admission, ICU admission diagnosis, and documented source of infection based on available microbiologic and virologic testing, including cultures and viral panel results. Clinical outcomes included vasopressor reinitiation, blood glucose readings, mechanical ventilation requirements, ICU and hospital length of stay, and ICU and hospital mortality.

Outcome Measures

The primary outcome of this study was hemodynamic instability post-corticosteroids discontinuation. Hemodynamic instability was defined as the reinitiation of vasopressors within 72 hours following abrupt discontinuation. For cases involving tapering, patients will be monitored throughout the tapering process and 72 hours after complete discontinuation to assess vasopressor reinitiation. Patients receiving chronic corticosteroid therapy for more than 1 month before ICU admission in both arms were followed until they transitioned from hydrocortisone to their regular corticosteroid regimen.

Secondary outcomes included glycemic control, mechanical ventilation requirements, length of stay in the ICU and hospital, and in-hospital and ICU mortality. Glycemic control was evaluated by documenting the maximum random blood glucose reading within 72 hours after abrupt discontinuation. For patients undergoing gradual tapering, the highest random blood glucose reading during tapering and within 72 hours after hydrocortisone discontinuation was recorded. Hyperglycemia was defined as a random blood glucose level of more than 10 mmol/L (180 mg/dL) and was evaluated during the same period (12, 13).

Statistical Analysis

A sample size of 400 patients was calculated to achieve a two-sided 95% CI with a width of 0.070, assuming a 15% prevalence of hemodynamic instability following hydrocortisone discontinuation (12, 13). Continuous variables were analyzed using the Student *t* test or Mann-Whitney *U* test, whereas categorical data were assessed with Pearson chi-square test or Fisher exact test. Simple logistic regression evaluated the association between discontinuation strategies and hemodynamic instability, followed by multiple logistic regression to adjust for confounders. Time-to-event analysis, from vasopressor discontinuation to reinitiation, was assessed with Kaplan-Meier curves and compared using the log-rank test. Hazard ratios (HRs) with 95% CIs were reported. A *p* value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS, Version 28 (IBM Corp., Armonk, NY).

RESULTS

Cohort Characteristics

A total of 1414 patients were screened for potential enrollment, of which 414 were included in the study. The primary reasons for exclusion were death before or during corticosteroids tapering (*n* = 388), corticosteroids use for less than 48 hours (*n* = 260), or corticosteroids discontinuation before vasopressors discontinuation (*n* = 146) (**Fig. 1**).

The median age of the included patients was 55.4 ± 17.1 years, with 55.6% being male. The most commonly reported comorbidities were hypertension (36.7%), malignancy (36.7%), and diabetes mellitus (35.7%). Chronic corticosteroid use, predominantly for organ transplantation or gastrointestinal conditions, was documented in 8.9% of patients. Sepsis was the primary cause of ICU admission in 47.2% of cases. The mean SOFA score for the cohort was 9.11. Positive cultures were identified in 55.5% of patients, with the bloodstream (52.6%) and respiratory tract (37.4%) being the most common sites of infection. Gram-negative bacteria were the most frequently identified organisms (77.0%). Other pathogens identified to a lesser extent included Gram-positive bacteria (28.3%), fungi (10.9%), and viruses (2.6%). Initial antimicrobial therapy was appropriate in 79.5% of patients with documented infections. The study cohort was divided into two groups based on hydrocortisone discontinuation strategy into gradual tapering (51.2%) and abrupt discontinuation (48.8%) groups (**Table S1**, https://links.lww.com/CCX/B531).

Regarding vasopressor usage, norepinephrine was the primary agent used across the cohort. Approximately 40% of patients required an additional vasopressor, with vasopressin being the second most frequently used agent. The maximum dose of vasopressors, expressed in norepinephrine equivalents, was similar between both groups, with a median dose of 0.20 µg/kg/min. However, patients in the gradual tapering group required a longer median duration of vasopressor therapy compared with those in the abrupt discontinuation group (82.5 vs. 65.0 hr, respectively; *p* = 0.001). In cases where two or more vasopressors were administered, vasopressin was mostly the first to be discontinued, occurring in 85.2% of cases (**Table 1**).

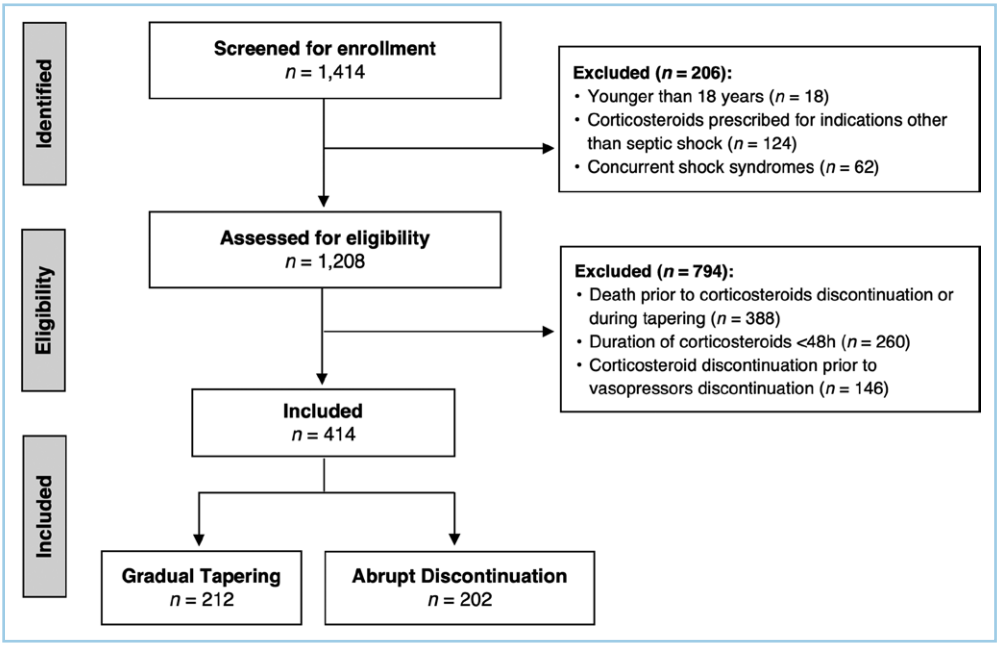
Identified
Screened for enrollment
n = 1,414
Excluded (n = 206):
• Younger than 18 years (n = 18)
• Corticosteroids prescribed for indications other than septic shock (n = 124)
• Concurrent shock syndromes (n = 62)
Eligibility
Assessed for eligibility
n = 1,208
Excluded (n = 794):
• Death prior to corticosteroids discontinuation or during tapering (n = 388)
• Duration of corticosteroids <48h (n = 260)
• Corticosteroid discontinuation prior to vasopressors discontinuation (n = 146)
Included
Included
n = 414
Gradual Tapering
n = 212
Abrupt Discontinuation
n = 202

Figure 1. Enrollment flowchart.

For corticosteroids use, hydrocortisone was initiated at an average of 5 hours after the initiation of vasopressors, with a 100 mg loading dose being administered at similar rates in both gradual tapering and abrupt discontinuation groups (49.1% vs. 42.6%, respectively; $p = 0.186$). Fludrocortisone was used less frequently, administered in only 4.1% of the overall cohort. The gradual tapering strategy resulted in a significantly longer median time from vasopressor discontinuation to hydrocortisone discontinuation (122.5 vs. 31.5 hr, respectively; $p < 0.001$) and a longer total duration of hydrocortisone therapy (8 vs. 3 d, respectively; $p < 0.001$), compared with abrupt discontinuation (Table 1).

Outcomes

In this study, gradual tapering of hydrocortisone was associated with a higher incidence of hemodynamic instability, as evidenced by a greater need for vasopressor reinitiation during or after tapering, compared with abrupt discontinuation (29.2% vs. 12.9%, respectively; $p < 0.001$) (**Table 2**). The unadjusted odds ratio (OR) for hemodynamic instability following hydrocortisone discontinuation indicated a lower risk with the abrupt discontinuation strategy (OR, 0.357; 95% CI, 0.21–0.59; $p < 0.001$). However, after adjusting for factors such as vasopressor therapy duration, hydrocortisone therapy duration, fludrocortisone use, and chronic steroid use, the total duration of hydrocortisone therapy emerged as the primary predictor of hemodynamic instability after discontinuation, regardless of the discontinuation method used (adjusted OR, 1.083; 95% CI, 1.025–1.145; $p = 0.004$) (**Table 3**).

The cumulative hazard plot (**Fig. 2**) visually illustrates the difference in vasopressor reinitiation risk between patients who discontinued hydrocortisone abruptly vs. those gradually using the tapering method. The analysis indicates that patients who discontinued hydrocortisone abruptly had a 61.4% lower risk of vasopressor reinitiation at any time during follow-up compared with those who were tapered gradually (HR, 0.386; 95% CI, 0.244–0.610; $p < 0.001$).

Regarding other clinical outcomes, the gradual tapering strategy was associated with a higher incidence of hyperglycemia (59.4% vs. 43.1%; $p < 0.001$) and a higher mean maximum blood glucose level (11.9 vs. 9.6 mmol/L; $p = 0.002$). This difference was more pronounced in diabetic patients (15.8 vs. 12.8 mmol/L; $p < 0.001$) compared with nondiabetics (9.0 vs. 8.0 mmol/L; $p = 0.08$). The number of patients requiring insulin therapy following hydrocortisone discontinuation was slightly higher in the tapering group than in the abrupt discontinuation, but the difference was not statistically significant (42.9% vs. 38.1%, respectively; $p = 0.319$). Similarly, the median daily insulin dose by 72 hours after discontinuation remained comparable between groups (15 vs. 18 international units [IUs]/d; $p = 0.634$), with no significant variation observed in diabetic (19 vs. 20 IU/d; $p = 0.732$) or nondiabetic patients (12.5 vs. 14 IU/d; $p = 0.692$). Additionally, gradual tapering was associated with longer durations of mechanical ventilation (11 vs. 8 d; $p = 0.014$) and ICU stay (13 vs. 10 d; $p = 0.008$) (Table 2).

DISCUSSION

In this retrospective cohort study, abrupt hydrocortisone discontinuation was linked to lower rates of hemodynamic instability post-discontinuation compared with gradual tapering. Additionally, the abrupt discontinuation strategy was associated with shorter steroid therapy duration by 5 days, along with shorter duration of mechanical ventilation, shorter ICU length of stay, and decreased incidence of dysglycemia, particularly in patients with diabetes, compared with the tapering group. Irrespective of discontinuation strategies, the total duration of hydrocortisone therapy emerged as the primary independent predictor of hemodynamic instability post-discontinuation.

Corticosteroids are essential for managing inflammation and shock but carry significant risks, including muscle weakness, hyperglycemia, infections, and ICU-acquired complications, which can prolong mechanical ventilation and ICU stays (16, 17). They suppress the hypothalamic-pituitary-adrenal (HPA) axis by inhibiting corticotropin-releasing hormone and adrenocorticotropic hormone, with the degree of suppression influenced by dose, duration, and potency (18–20).

Prolonged corticosteroid therapy in critically ill patients can lead to hemodynamic instability upon discontinuation through multiple mechanisms. Suppression of the HPA axis reduces endogenous

TABLE 1.
Vasopressor and Corticosteroids Usage Patterns Among Septic Shock Patients[a]

Characteristic	Overall (*n* = 414)	Gradual Tapering (*n* = 212)	Abrupt Discontinuation (*n* = 202)	*p*[b]
Vasopressors used				
Norepinephrine	414 (100.0)	212 (100.0)	202 (100.0)	
Vasopressin	159 (38.4)	83 (39.2)	76 (37.6)	0.749
Epinephrine	9 (2.2)	4 (1.9)	5 (2.5)	0.746[c]
Dopamine	10 (2.4)	5 (2.4)	5 (2.5)	0.999[c]
Phenylephrine	2 (0.5)	2 (0.9)	0 (0.0)	0.499[c]
Number of vasopressors used				
1	245 (59.2)	124 (58.5)	121 (59.9)	0.621[c]
2	162 (39.1)	83 (39.2)	79 (39.1)	
≥ 3	7 (1.7)	5 (2.4)	2 (1.0)	
Duration of vasopressors therapy (hr)	73.0 (45–112)	82.5 (50–135)	65.0 (44–97)	0.001
Maximum dose of vasopressors in norepinephrine equivalents (µg/kg/min)[e]	0.20 (0.11–0.39)	0.24 (0.10–0.39)	0.20 (0.12–0.38)	0.808[d]
Order of vasopressors discontinuation[f]				
Vasopressin first	17 (10.6)	8 (10.9)	9 (11.8)	0.653
Norepinephrine first	142 (89.3)	75 (89.1)	67 (88.1)	
Median time from vasopressors initiation to steroid initiation (hr)	5.0 (3.0–18.0)	5.0 (3.0–18.50)	5.0 (3.0–17.00)	0.697[d]
Loading dose of hydrocortisone (100 mg)	190 (45.9)	104 (49.1)	86 (42.6)	0.186
Use of fludrocortisone	17 (4.1)	10 (4.7)	7 (3.5)	0.521
Total duration of corticosteroids (d)	5.0 (3.0–9.0)	8.0 (5.0–13.0)	3.0 (2.0–5.0)	< 0.001[d]
Duration of corticosteroids taper (d)	NA	3.0 (2.0–5.0)	NA	NA

NA = not applicable.

[a]Results are expressed as median (interquartile range) and *n* (%).

[b]*p* value has been calculated using Pearson χ^2 *t* test.

[c]*p* value has been calculated using Fisher exact test.

[d]*p* value has been calculated using Mann-Whitney *U* test.

[e]Norepinephrine equivalent (µg/kg/min) = (epinephrine [µg/kg/min] × 1) + (dopamine [µg/kg/min] × 1/100) + (phenylephrine [µg/kg/min] × 0.06) + (vasopressin [U/min] × 2.5) + (angiotensin II [ng/kg/min] × 0.0025) + (terlipressin [µg/kg/min] × 10) + (methylene blue [mg/kg/hr] × 0.2) + (metaraminol [µg/kg/min] × 8) + (midodrine [µg/kg/min] × 0.4) + (hydroxocobalamin [g] × 0.02) (15).

[f]Percentages were calculated using the total number of patients that received vasopressin as the denominator.

cortisol production, impairing vascular tone and catecholamine responsiveness, which may exacerbate hemodynamic instability, especially after prolonged corticosteroid use beyond 2–3 weeks (20–22). Additionally, corticosteroids with mineralocorticoid activity promote sodium retention and fluid shifts, which can obscure hypovolemia and contribute to hemodynamic deterioration (19, 23, 24). While fluid retention has been implicated in worsening cardiac function, this association may be confounded by indication bias, as patients with greater severity of illness are more likely to receive corticosteroids (24, 25). Another key factor to consider is rebound inflammation, where abrupt corticosteroid withdrawal triggers a surge in proinflammatory cytokines, potentially worsening vasodilatory shock and increasing vasopressor requirements. This has been observed in conditions such as COVID-19 (26, 27). Although gradual tapering is often recommended to mitigate these risks, evidence in critically ill patients remains inconclusive,

TABLE 2.
Primary and Secondary Outcomes[a]

Characteristic	Total ($n = 414$)	Gradual Tapering ($n = 212$)	Abrupt Discontinuation ($n = 202$)	p[b]
Primary outcome				
Vasopressors reinitiation during tapering or within 72 hr after hydrocortisone discontinuation	88 (21.3)	62 (29.2)	26 (12.9)	< 0.001
Secondary outcomes				
Hyperglycemia (> 10 mmol/L) during tapering or within 72 hr after hydrocortisone discontinuation	213 (51.4)	126 (59.4)	87 (43.1)	< 0.001
Maximum random blood glucose reading during tapering or within 72 hr after hydrocortisone discontinuation (mmol/L)				
Total	10.7 (7.2–14.5)	11.9 (8.0–15.7)	9.6 (7.0–13.3)	0.002[c]
Diabetic population	14.5 (11.7–17.3)	15.8 (14.0–18.3)	12.8 (9.8–15.5)	< 0.001[c]
Nondiabetic population	8.1 (7.0–12.2)	9.0 (7.0–12.6)	8.0 (7.0–11.1)	0.08[c]
Number of patients requiring insulin therapy by 72 hr after hydrocortisone discontinuation	168 (40.5)	91 (42.9)	77 (38.1)	0.319
Median daily dose of insulin therapy by 72 hr after hydrocortisone discontinuation in patients receiving insulin therapy (interquartile range)				
Total	16 (10–26)	15 (10–25)	18 (10–28.5)	0.634[c]
Diabetic population	20 (12–28)	19 (12–26)	20 (10–30)	0.732[c]
Nondiabetic population	13 (8.25–21.5)	12.5 (8.75–18)	14 (6.75–23)	0.692[c]
Mechanical ventilation	304 (73.4)	157 (74.1)	147 (72.8)	0.767
Duration of mechanical ventilation (d)	9.0 (3.7–24.0)	11.0 (5.0–26.0)	8.0 (3.0–19.0)	0.014[c]
ICU length of stay (d)	12.0 (5.0–26.0)	13.0 (6.5–28.0)	10.0 (4.0–22.0)	0.008[c]
Hospital length of stay (d)	38.0 (21.7–65.2)	39.0 (22.5–68.5)	37.0 (21.0–61.0)	0.340[c]
ICU mortality	103 (24.9)	60 (28.3)	43 (21.3)	0.099
Hospital mortality	141 (34.1)	75 (35.4)	66 (32.7)	0.562

[a]Results are expressed as median (interquartile range) and *n* (%).
[b]*p* value has been calculated using Pearson χ^2 *t* test.
[c]*p* value has been calculated using Mann-Whitney *U* test.

with no clear advantage over abrupt discontinuation in improving hemodynamic outcomes.

The Annane, activated protein C and corticosteroids for human septic shock, and adjunctive corticosteroid treatment in critically Ill patients with septic shock trials used a 7-day hydrocortisone regimen with abrupt discontinuation (5–8), while the corticosteroid therapy of septic shock and hydrocortisone for prevention of septic shock trials tapered over 6 days following 5 days of therapy for a total of 11 days (7, 28). The rationale behind the gradual tapering of hydrocortisone in these trials was the concern for an increase in proinflammatory mediators and hemodynamic deterioration after the abrupt discontinuation of corticosteroids (29). In our cohort, a similar approach was observed. Patients in the tapering group had corticosteroids tapered over a median of 3 days, resulting in a significantly longer total duration of corticosteroid therapy, 8 days compared with 3 days in the abrupt discontinuation group ($p < 0.001$). This extended exposure may have contributed to greater hemodynamic instability, potentially reflecting the impact of prolonged corticosteroid use.

To our knowledge, only two small retrospective studies compared steroid discontinuation strategies

TABLE 3.
Independent Factors Associated With Vasopressors Reinitiation During Tapering or Within 72 Hours of Hydrocortisone Among Patients With Septic Shock (*n* = 414)

	Unadjusted		Adjusted	
Characteristic	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Abrupt discontinuation of corticosteroids	0.357 (0.21–0.59)	< 0.001	0.609 (0.336–1.104)	0.102
Duration of corticosteroids (d)[a]	1.110 (1.066–1.156)	< 0.001	1.083 (1.025–1.145)	0.004
Use of chronic steroids (> 1 mo)	0.303 (0.091–1.011)	0.052	0.291 (0.082–1.037)	0.057
Use of fludrocortisone	1.147 (0.364–3.607)	0.815	1.163 (0.351–3.849)	0.805
Duration of vasopressors (hr)[a]	1.003 (1.001–1.005)	0.001	1.001 (0.998–1.003)	0.604
Maximum dose of vasopressors in norepinephrine equivalents (μg/kg/min)[a]	1.164 (0.495–2.740)	0.728	1.100 (0.400–3.031)	0.853

OR = odds ratio (adjusted for all other variables in the table).
[a]OR for vasopressor dose reflects change per 1 μg/kg/min norepinephrine equivalent; OR for corticosteroid duration reflects change per 1 d; and OR for vasopressor duration reflects change per 1 hr.
Multiple logistic regression analyses.

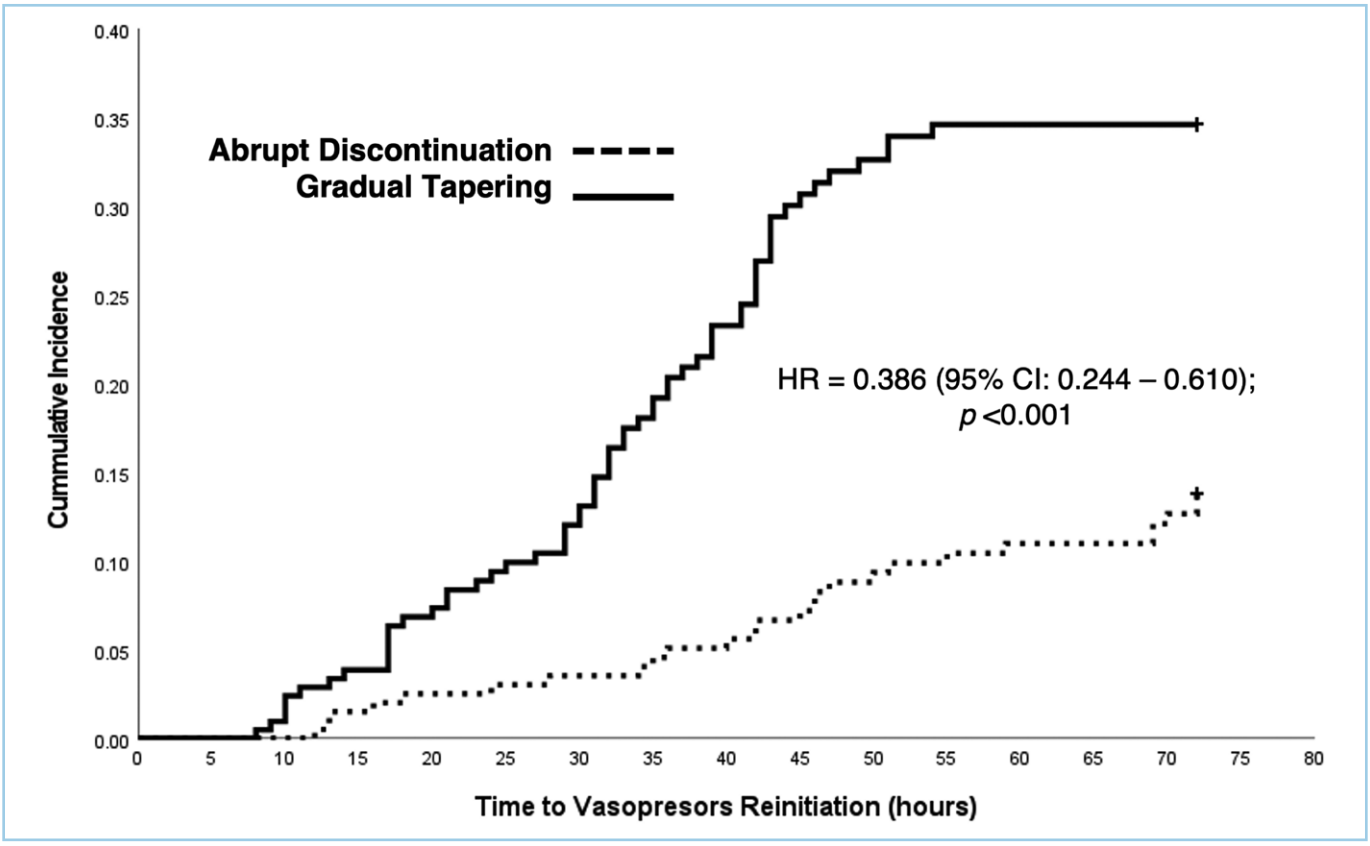

Figure 2. *Cumulative hazard plot* of vasopressor reinitiation following abrupt and gradual hydrocortisone discontinuation. Time zero was defined as the time of vasopressor discontinuation. HR = hazard ratio.

among patients with septic shock (12, 13). There are key distinctions between our study population and those described in prior literature. Notably, our study population had lower SOFA scores (12 vs. 9), required lower maximum vasopressor doses (0.29 vs. 0.20 μg/kg/min), but longer median duration of vasopressor therapy (73 vs. 60 hr) compared with previously studied cohorts (12, 13). Despite these differences, we

observed significantly higher overall rates of hemodynamic instability during hydrocortisone tapering or discontinuation compared with previous reports. This is likely due to the overall longer duration of hydrocortisone therapy across our study cohort and the inclusion of a larger and more diverse patient population.

While our study identified an association between tapering and higher hemodynamic instability, the observed trend toward higher mortality did not reach statistical significance, possibly due to limited sample size and insufficient power to detect differences in this secondary outcome. Similarly, an individual patient data meta-analysis evaluating corticosteroid discontinuation strategies in septic shock found no significant difference in mortality between gradual tapering and abrupt discontinuation of hydrocortisone (30). These findings collectively suggest that while discontinuation strategies play a critical role in hemodynamic stability, their direct impact on mortality remains unproven and warrants further investigation through prospective trials.

Additionally, we identified higher rates of dysglycemia, particularly among diabetic patients. While prior studies reported conflicting results on glycemic control, our findings further highlight the link between gradual tapering and increased dysglycemia, which may be related to the longer duration of steroid therapy in the tapering group (12, 13). Despite differences in hyperglycemia incidence and maximum blood glucose levels, insulin requirements remained comparable between the groups, even after stratification by diabetes status. Although fewer patients in the abrupt discontinuation group required insulin during follow-up, those who did had slightly higher insulin dose requirements. However, these differences were not statistically significant and may be explained by the slightly higher proportion of diabetic patients in the abrupt discontinuation group. Our findings align with those of Carabetta et al (13), who also observed higher glucose levels in the tapering group compared with abrupt discontinuation, but no statistically significant difference in insulin requirements. While the mechanism remains unclear, the transient dysglycemia associated with steroid tapering appears to be clinically insignificant and does not necessarily translate to increased insulin use, possibly due to adaptive glycemic regulation or differences in cumulative steroid exposure (31).

Beyond glycemic effects, our study builds on the findings of Carabetta et al (13), who observed a trend toward longer ICU stays in the tapering group, although this was not statistically significant, likely due to their smaller sample size (9 vs. 7.6 d; $p = 0.62$). In contrast, our larger cohort showed a statistically significant prolongation of ICU stay, with the tapering group experiencing an average increase of 3 days (13 vs. 10 d; $p = 0.008$).

Our study uniquely included patients receiving chronic steroids, representing 8.9% of the total cohort, a group underrepresented in prior studies. Notably, more patients in the abrupt discontinuation group were on chronic corticosteroids compared to the tapering group, although this difference was numerical and not statistically significant. Furthermore, in our multivariate model assessing independent risk factors for vasopressor reinitiation, we observed trends toward reduced risk in the abrupt discontinuation group. This may be attributed to patients typically being transitioned to their home dose of corticosteroids rather than complete discontinuation, which could mitigate the risk of hemodynamic instability.

Our study has several notable strengths. First, it is the largest investigation to date assessing hydrocortisone discontinuation strategies in septic shock with a sample size more than double that of prior studies. By including multiple ICUs within a single center, we enhance external validity and capture a broader patient population, supporting the generalizability of our findings. Additionally, our study provides a comprehensive evaluation of hemodynamic instability, incorporating key variables such as the duration of corticosteroid therapy, chronic corticosteroid use, and vasopressor duration for the first time. Beyond this, we expand on previous research by examining additional clinical outcomes, including duration of mechanical ventilation, ICU mortality, and incidence of hyperglycemia in both diabetic and nondiabetic patients. These factors together reinforce the depth and impact of our findings.

Several limitations of this study must be acknowledged. Its retrospective, single-center design introduces potential biases, such as selection and documentation bias, limiting causal inference and generalizability, particularly to older patient populations commonly encountered in the United States and other countries. Additionally, provider discretion in the timing and methods of corticosteroid discontinuation may have introduced variability in treatment approaches. The wide range of corticosteroid treatment durations further complicates the interpretation

of outcomes and warrants caution when drawing generalizable conclusions.

A key methodological challenge is the variation in follow-up periods for hemodynamic instability, which is inherently tied to treatment duration. Longer corticosteroid exposure in the tapering group may have inflated the reported incidence simply due to extended monitoring. However, this limitation has been consistently observed in retrospective studies, including those by Sobolewski et al (12) and Carabetta et al (13). Given that all published studies on this topic share this issue, prospective trials with standardized follow-up durations are essential to minimize bias and provide a more definitive comparison of hemodynamic outcomes between tapering strategies.

Another consideration is the exclusion of patients who died before corticosteroids tapering or discontinuation, which may limit generalizability by omitting the most critically ill individuals receiving corticosteroids for septic shock. However, their inclusion was not feasible, as early mortality prevented assessment of the primary endpoint, and their clinical course was likely driven by factors beyond the discontinuation strategy. This limitation has also been addressed in prior research using similar exclusion criteria to ensure meaningful comparisons (12, 13). The retrospective nature of the study limited our ability to systematically identify secondary infections, viral reactivation, or unresolved primary infections, which may have influenced the observed clinical outcomes. Additionally, the assumption that morbidity levels were similar between groups at the time of steroid cessation, based on vasopressor discontinuation, may have influenced the results.

Despite these limitations, we believe our findings are hypothesis-generating and provide valuable insight into corticosteroid discontinuation strategies in septic shock. Future prospective randomized controlled trials are needed to further explore this question and strengthen the evidence base for optimal corticosteroid discontinuation approaches.

CONCLUSIONS

Our study provides valuable insights into corticosteroid discontinuation strategies in patients recovering from septic shock, highlighting that while abrupt hydrocortisone discontinuation was associated with fewer ICU-related complications, the overall duration of corticosteroid therapy emerged as the primary factor linked to increased risk of hemodynamic instability. These findings emphasize the importance of minimizing unnecessary corticosteroid exposure to mitigate risks in critically ill patients. This study contributes to the existing body of literature and emphasizes the need for future prospective randomized trials to define the optimal duration and approach to corticosteroid discontinuation in this population.

ACKNOWLEDGMENTS

We thank Ms. Fatima AlMulhim for her valuable assistance with data analysis.

1 *Pharmaceutical Care Division, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.*

2 *Epidemiology and Biostatistics Administration, Population Health Management, King Fahad Specialist Hospital, Eastern Province, Saudi Arabia.*

3 *Department of Critical Care Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.*

4 *Pharmacy Department, King Fahad Specialist Hospital, Eastern Province, Saudi Arabia.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: Nalqadheeb@moh.gov.sa

REFERENCES

1. Martin G: Sepsis, severe sepsis, and septic shock: Changes in incidence, pathogens, and outcomes. *Expert Rev Anti Infect Ther* 2012; 10:701–706
2. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810
3. Paoli CJ, Reynolds MA, Sinha M, et al: Epidemiology and costs of sepsis in the United States: An analysis based on timing of diagnosis and severity level. *Crit Care Med* 2018; 46:1889–1897
4. Evans L, Rhodes A, Alhazzani W, et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:1063–1143
5. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
6. Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378:809–818

7. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
8. Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378:797–808
9. Burry LD, Williamson D, Steinberg M: Role of corticosteroids in septic shock. *Ann Pharmacother* 2004; 38:464–472
10. Annane D, Sébille V, Troché G, et al: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotrophin. *JAMA* 2000; 283:1038–1045
11. Chaudhuri D, Nei AM, Rochwerg B, et al: 2024 Focused update: Guidelines on use of corticosteroids in sepsis, acute respiratory distress syndrome, and community-acquired pneumonia. *Crit Care Med* 2024; 52:e219–e233
12. Sobolewski KA, Bakshi A, O'Connor Y, et al: Abrupt versus gradual cessation of steroids in patients with septic shock. *J Crit Care* 2018; 48:198–202
13. Carabetta S, Azar B, Carleton C, et al: Abrupt discontinuation versus taper of hydrocortisone in patients with septic shock. *Ann Pharmacother* 2023; 57:375–381
14. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
15. Kotani Y, Hashimoto A, Taniguchi M, et al: An updated "norepinephrine equivalent" score in intensive care as a marker of shock severity. *Crit Care* 2023; 27:29
16. van Paassen J, Vos P, Vanderbeke L, et al: Corticosteroid use in COVID-19 patients: A systematic review and meta-analysis on clinical outcomes. *Crit Care* 2020; 24:696
17. Pastores SM: Steroids in the acutely ill: Evolving recommendations and practice. *Cleve Clin J Med* 2022; 89:505–511
18. Silverman MN, Sternberg EM: Glucocorticoid regulation of inflammation and its functional correlates: From HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci* 2012; 1261:55–63
19. Bornstein SR, Allolio B, Arlt W, et al: Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2019; 104:247–256
20. Broersen LH, Pereira AM, Jørgensen JO, et al: Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015; 100:2171–2180
21. Husebye ES, Allolio B, Arlt W, et al: Consensus statement on the diagnosis, treatment, and follow-up of patients with primary adrenal insufficiency. *J Intern Med* 2018; 284:637–645
22. Marik PE: Critical illness-related corticosteroid insufficiency. *Chest* 2009; 135:181–193
23. Annane D, Pastores SM, Rochwerg B, et al: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017; 43:1751–1763
24. Haan BJ, Blackmon SN, Cobb AM, et al: Corticosteroids in critically ill patients: A narrative review. *Pharmacotherapy* 2024; 44:581–602
25. Frenkel A, Abuhasira R, Bichovsky Y, et al: Examination of the association of steroids with fluid accumulation in critically ill patients, considering the possibility of biases. *Sci Rep* 2021; 11:5557
26. Murakami K, Sano H, Tode N, et al: Clinical features of COVID-19 patients with rebound phenomenon after corticosteroid therapy. *BMJ Open Respir Res* 2022; 9:e001332
27. Tran H, Vu VH, Phan TT, et al: A case of rebound inflammation in a 38-year-old man with severe COVID-19 pneumonia following cessation of dexamethasone therapy. *Am J Case Rep* 2022; 23:e935946
28. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of hydrocortisone on development of shock among patients with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016; 316:1775–1785
29. Keh D, Boehnke T, Weber-Cartens S, et al: Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: A double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520
30. Pirracchio R, Annane D, Waschka AK, et al: Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. *NEJM Evid* 2023; 2:EVIDoa2300034
31. Rafacho A, Ortsäter H, Nadal A, et al: Glucocorticoid treatment and endocrine pancreas function: Implications for glucose homeostasis, insulin resistance and diabetes. *J Endocrinol* 2014; 223:R49–R62